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# The prognostic value of fixed time and self-paced walking tests in patients diagnosed with idiopathic pulmonary fibrosis

## Abstract

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic fibrosing interstitial pneumonia that has an unknown etiology. The natural history of the disease is characterized by a progressive decline in pulmonary function and overall health and well-being. The median survival time is between 2–3 years; however, the disease course is variable and unpredictable.

The twelve-minute walking test (12MWT) and six-minute walking test (6MWT) are two fixed time tests that are commonly used in clinical practice. Our short and clinically oriented narrative review attempted to summarize current evidence supporting the use of fixed time, self-paced walking tests in predicting the outcome of patients diagnosed with IPF.

A number of studies have justified that the 6MWT is a simple, cost-effective, well documented, fixed time, and self-paced walking test which is a valid and reliable measure of disease status and can also be used as a prognostic tool in patients with IPF. However, there is a need for dedicated and validated reference equations for this population of patients.

It is also necessary to fill the knowledge gap about the role of the 12MWT. We hypothesize that it would be useful in evaluating patients that are in the early stages of the disease.

**Key words:** idiopathic pulmonary fibrosis, walking tests, 6MWT, 12MWT, Cooper test

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## Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic fibrosing interstitial pneumonia with an unknown etiology representing one of the most common entities of the heterogeneous group of interstitial lung diseases (ILDs). The prevalence of this rare disease is estimated to be at 2–29 cases per 100,000 in the general population [1–5]. The natural history of the disease is characterized by a progressive decline in pulmonary function as well as overall health and well-being. The median survival time is between 2–3 years but the disease course is variable and unpredictable [6–9].

The most common symptoms of this progressive disease include exertional dyspnea and

dry cough. The symptoms usually appear insidiously and many patients are unable to pinpoint the date of their appearance. It is important to note that deteriorating exercise tolerance often fails to alarm patients about the early stages of IPF because these patients tend to attribute their symptoms to the ageing process or treat them as a consequence of long-term tobacco smoking [10].

Progression dynamics clearly have an effect on the prognosis in IPF. Objective measurement of exercise capacity is one of the ways to monitor the disease course [11].

Cardiopulmonary exercise testing (CPET) is an objective assessment of exercise capacity and, in recent times, has become a more commonly used tool in clinical settings. However, CPET

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involves the use of specialized facilities that are not universally available. That is why simple fixed time and self-paced walking tests are more frequently used in the clinical assessment of exercise capacity. The twelve-minute walking test (12MWT) and six-minute walking test (6MWT) are two fixed time tests commonly used in clinical practice.

Our short and clinically oriented narrative review attempted to summarize current evidence supporting the use of fixed time and self-paced walking tests in predicting the outcome for patients diagnosed with IPF.

### Selected aspects of exercise pathophysiology in fibrotic interstitial lung diseases

The background of exercise intolerance in IPF patients is a complex, multidimensional, and multi-faceted issue. Most of the previous studies on exercise intolerance in patients with ILDs were performed on broad ILD populations which also included patients suffering from other fibrotic interstitial lung diseases, not only IPF. That being said, we may assume that these entities are comparable because the disease mechanisms involve a fibrotic process. From a pathophysiological point of view, fibrotic changes in the lungs lead to decreased lung compliance, which in turn results in an increased work of breathing and decreased lung volumes. These abnormalities present clinically as a classic restrictive pattern of lung disease. Patients develop a decreased total lung capacity, vital capacity, and inspirational capacity. These, in turn, result in a decreased tidal volume and an increased respiratory rate which leads to increased ventilation and, eventually, hypocapnia. Alveolar-capillary membrane thickening causes decreased oxygen diffusion and a ventilation-perfusion mismatch. In order to compensate for the resulting hypoxemia, the body increases ventilation. Clinically, hypoxemia is associated with a sensation of dyspnea. It also results in the constriction of pulmonary vessels and a subsequent decrease in cardiac output which leads to decreased delivery of oxygen to the muscles and resulting fatigue. IPF patients commonly present with weakness of the musculature of the lower limbs which contributes to exercise intolerance. It is important to mention that pulmonary microvasculopathy also contributes to decreased cardiac output. These vascular changes are a result of endothelial proliferation, remodeling, and capillary obliteration. Decreased oxygen delivery to the muscles will also result in

increased oxygen extraction and, subsequently, decreased venous oxygen capacity which potentiates hypoxemia [12–29].

In summary, the complex aforementioned mechanisms lead to primary symptoms of dyspnea and fatigue which, together, form the basis of exercise intolerance.

### General principles of the 12MWT and the 6MWT

The 12MWT is based on a 12-minute performance test introduced by Cooper *et al.* as a guide to determine the state of physical fitness in healthy young men [30]. The authors observed that field testing can provide a good assessment of maximal oxygen consumption in young and well-motivated subjects. However, the accuracy of the estimate is related directly to the motivation of the subjects [30]. The test requires the patient to cover the maximum possible distance in 12 minutes by running, walking, or using a combination of both [31]. Results of the 12MWT are highly reproducible [32]. The prediction of cardiorespiratory fitness in this test is described by the following equation [31]:  $\text{VO}_{2\text{max}} (\text{mL/kg/min}) = (\text{distance [m]} - 504.9)/44.73$ .

The 6MWT is considered a simple, cost-effective, and well-documented field test for the assessment of the functional exercise capacity. It can also be used to assess the response to medical interventions in various diseases. It was introduced as a therapeutic tool in respiratory medicine by Butland *et al.* [33] in their study comparing three fixed time tests (2-, 6-, and 12-minute walking tests) and they concluded that shorter distance tests would be just as beneficial as the 12MWT. The authors also observed high correlation coefficients between the 2-, 6-, and 12-minute tests. This indicates that they were similar measures of exercise tolerance. All of these tests showed equal reproducibility. However, the longer tests presented a greater discrimination than the shorter ones [33]. Therefore, the 6MWT seems to be a satisfactory compromise between test validity and patient acceptability. Nowadays, this is the most common fixed distance test used in clinical and research settings.

Mänttari *et al.* observed that the 6MWT performed on a 15 m track may predict a  $\text{VO}_{2\text{max}}$  in healthy adults with an accuracy of about 1 metabolic equivalent (MET). The following equations were proposed [34]:

— For men:

$$\text{VO}_{2\text{max}} (\text{mL/kg/min}) = 110.546 + 0.063 \times \text{distance} - 0.250 \times \text{age} - 0.486 \times \text{BMI} - 0.42 \times$$

height [cm] – 0.109 × heart rate at the end of the test,

— For women:

$\text{VO}_2\text{max (mL/kg/min)} = 22.506 - 0.271 \times \text{weight} + 0.051 \times \text{distance} - 0.065 \times \text{age}.$

### **The prognostic value of the 12MWT and the 6MWT in IPF**

The 12MWT is less commonly used for IPF patients because it requires greater effort by the patient than the 6MWT. We hypothesize that it would be useful in evaluating patients in the early stages of the disease. However, it is important to mention that our research is currently in progress and that this is only a running hypothesis.

On the other hand, there is a growing body of evidence supporting the role of the 6MWT in the evaluation of IPF patients. Caminati *et al.* [35] performed a retrospective analysis of 44 patients with IPF of whom 29 had an additional evaluation at follow-up after 12 months. During a mean follow-up period of 19.8 months, 11 patients died because of IPF. The authors observed that the distance walked in 6 minutes (6MWD) was independently related to mortality and that patients who walked less than 212 meters had a significantly lower survival rate than those who were able to walk a longer distance. Changes in distance walked upon evaluation at 12 months were also predictive of survival. Du Bois *et al.* aimed to assess the reliability, validity, and responsiveness of the 6MWD. At the conclusion of their study, they estimated the minimal clinically important difference in IPF patients as 24–45 m [36]. The 6MWD was measured at baseline and at 24-week intervals. A comparison of two proximal measures of the 6MWD demonstrated good reliability. As was previously cited in the Caminati *et al.* study, these authors also observed that a change in the results of the 6MWD was highly predictive of mortality. Moreover, test results weakly correlated with forced vital capacity, diffusion capacity of the lung for carbon monoxide, resting alveolar–arterial gradient, and health-related quality of life. Measured values were consistently and significantly lower for patients with the poorest functional status. For example, a patient who, at baseline, covered a distance of less than 250 m was associated with a 2.65-fold increased risk of death over the following year when compared with a patient who was able to cover a distance of more than 350m. On the flip side, a decline in distance covered of 50 meters or more was associated with a 4.27-fold increased risk of death over

the following year when compared with patients whose deterioration was capped at a maximum of 25 meters [36]. Three years later, the authors published another paper in which they proved that both the 6MWD and resulting changes in 6MWD results were independent predictors of mortality in patients with IPF [37].

Moreover, in a study of 197 patients conducted by Flaherty *et al.*, the authors observed that desaturation during the 6MWT was associated with an increased mortality rate even though a threshold of 88% was not reached. Moreover, for patients with a baseline saturation of 88% or less, the strongest observed predictor of mortality was a serial change in the lung transfer factor for carbon monoxide. However, for patients who had a saturation over 88% during their baseline walking test, serial decreases in forced vital capacity (FVC) and increases in desaturation area significantly predicted subsequent mortality [38].

Another interesting and clinically important study was performed by Lederer *et al.* who analyzed the association between the 6MWD and survival in 454 patients with IPF who were listed for lung transplantation. This study showed that a shorter 6MWD result was associated with an increased mortality rate. Moreover, patients who covered a distance of less than 207m had a four-fold greater mortality rate even after adjusting for demographics, anthropomorphic measurements, FVC expressed as percent of predicted, pulmonary hypertension, and medical comorbidities. They stated that the 6MWD was a significantly better predictor of six-month mortality than FVC expressed as a percent of predicted value [39].

Kozu *et al.* [40], in their prospective, cross-sectional observational study, assessed the relationship between the Medical Research Council (MRC) dyspnea grade and peripheral muscle force, activities of daily living performance, health status, lung function, and exercise capacity in 65 IPF patients in a stable clinical state. The authors noted a strong association between MRC grade and the 6MWD. Similarly, Manali *et al.* [41] prospectively studied the relationship between the MRC chronic Dyspnea Scale with cardiopulmonary exercise testing (CPET) and the 6MWT in 25 IPF patients. They found significant correlations between the MRC score and the following parameters of the 6MWT: distance walked,  $\text{SpO}_2$  at initiation and at the end of the test, and the difference in saturation before and after the test. Correlations with the pulse at the initiation and at the end of the test, the blood pressure,

and the Borg dyspnea scale were not significant. A multiple stepwise logistic regression analysis that tested a number of physiologic parameters showed that the only variable independently related to the MRC score was the distance walked at the 6MWT.

### Confounding factors

A considerable number of factors, both internal and external, can affect the result of the 6MWT. That is why a low 6MWD may be non-specific and non-diagnostic. In the event of a low 6MWT test result, it is important to further research whether or not such a result is reliable and accurate. Moreover, it would be helpful to analyze the 6MWT results in the context of pulmonary function tests, cardiac function, nutritional status, muscle strength, ankle-brachial index, orthopedic function, and cognitive function. From a constitutional point of view, age, height, weight, and sex independently affect the 6MWD in healthy adults [42]. It is important to note that a shorter walking corridor, decreased patient motivation, comorbidities, medications, oxygen supplementation, and previous experience with the test can affect the result [43]. This information highlights the need for specific reference equations.

### Reference equations

There are some reference equations for the 6MWT published in literature [44–52] which are not validated for the IPF population. However, in this context, it is worth to discuss a prospective, non-randomized controlled study conducted by Igarashi *et al.* In this study, the authors investigated the effect of an outpatient pulmonary rehabilitation program and the use of 6MWD (expressed as a percentage of the predicted value) to quantify the response to pulmonary rehabilitation in elderly patients with ILDs. They concluded that 6MWD, expressed as a percentage of the predicted value, might be more useful than the absolute 6MWD as an outcome measure of pulmonary rehabilitation, and as a predictor of response to pulmonary rehabilitation in elderly patients with ILDs [53]. The authors used reference equations proposed by Enright *et al.* [52].

Therefore, the body of evidence regarding the reference equations for the 6MWT in IPF shows that there are considerable gaps of knowledge in this area and highlights the need for comprehensive exploration of this topic.

### Conclusions

The 6MWT is a simple, cost-effective, well-documented, fixed time, and self-paced walking test evaluating functional capacity which is broadly used for clinical and research purposes. The 6MWT result is a valid and reliable measure of disease status and prognosis in patients with IPF. Nevertheless, there is a need to establish dedicated and validated reference equations for this population of patients.

There is also a need to fill the knowledge gap regarding the role of the 12MWT in this population. We hypothesize that it would be useful in evaluating patients in the early stages of the disease.

### Conflict of interest

None declared.

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